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G01N 33/50, A61K 35/00, 38/00, 39/00

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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,  
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ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Declarations under Rule 4.17:**

— as to the applicant's entitlement to claim the priority of the  
earlier application (Rule 4.17(iii)) for the following desig-  
nations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,  
BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC,  
EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,  
JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,  
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TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO  
patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG,  
ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU,  
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DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT,  
RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

— as to the applicant's entitlement to claim the priority of the  
earlier application (Rule 4.17(iii)) for the following desig-  
nations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY,  
BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC,  
EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS,  
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,  
MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG,  
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,  
TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW,  
ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ,  
UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD,  
RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ,  
DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL,  
PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI,  
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For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: METHOD FOR DIAGNOSING CHRONIC MYELOID LEUKEMIA

(57) Abstract: Objective methods for detecting and diagnosing Chronic myeloid leukemia (CML) are described herein. In one embodiment, the diagnostic method involves the determining a expression level of CML-associated gene that discriminate between CML and normal cell. The present invention further provides methods of screening for therapeutic agents useful in the treatment of CML, methods of treating CML and method of vaccinating a subject against CML.

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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 03/10256

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68 G01N33/50 A61K35/00 A61K38/00 A61K39/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, EMBL

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	LI HUIYU ET AL: "CDNA microarray analysis of chronic myeloid leukemia." INTERNATIONAL JOURNAL OF HEMATOLOGY. IRELAND MAY 2002, vol. 75, no. 4, May 2002 (2002-05), pages 388-393, XP009020831 ISSN: 0925-5710 the whole document	1
X	OHMINE K ET AL: "CHARACTERIZATION OF STAGE PROGRESSION IN CHRONIC MYELOID LEUKEMIA BY DNA MICROARRAY WITH PURIFIED HEMATOPOIETIC STEM CELLS" ONCOGENE, BASINGSTOKE, HANTS, GB, vol. 20, no. 57, 2001, pages 8249-8257, XP002952628 ISSN: 0950-9232 the whole document	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

13 November 2003

Date of mailing of the international search report

25.05.04

Name and mailing address of the ISA

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Rutz, B

## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 03/10256

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE EMBL 'Online! 10 August 1993 (1993-08-10), XP002261375 retrieved from EBI Database accession no. X16545 cited in the application abstract	21,22
A	MAEDA TAKASHI ET AL: "Growth inhibition of mammalian cells by eosinophil cationic protein." EUROPEAN JOURNAL OF BIOCHEMISTRY / FEBS. GERMANY JAN 2002, vol. 269, no. 1, January 2002 (2002-01), pages 307-316, XP002261370 ISSN: 0014-2956 abstract; table 1	26
A	KANETA YASUYUKI ET AL: "Prediction of sensitivity to STI571 among chronic myeloid leukemia patients by genome-wide cDNA microarray analysis." JAPANESE JOURNAL OF CANCER RESEARCH: GANN. JAPAN AUG 2002, vol. 93, no. 8, August 2002 (2002-08), pages 849-856, XP002260979 ISSN: 0910-5050	
A	DELILIERIS GIORGIO LAMBERTENGHI ET AL: "Effect of inositol hexaphosphate (IP(6)) on human normal and leukaemic haematopoietic cells." BRITISH JOURNAL OF HAEMATOLOGY. ENGLAND JUN 2002, vol. 117, no. 3, June 2002 (2002-06), pages 577-587, XP002261371 ISSN: 0007-1048	
A	COHEN N ET AL: "Subgroup of patients with Philadelphia-positive chronic myelogenous leukemia characterized by a deletion of 9q proximal to ABL gene: expression profiling, resistance to interferon therapy, and poor prognosis." CANCER GENETICS AND CYTOGENETICS. UNITED STATES 15 JUL 2001, vol. 128, no. 2, 15 July 2001 (2001-07-15), pages 114-119, XP002261372 ISSN: 0165-4608	
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## INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 03/10256

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	MIYAZATO A ET AL: "IDENTIFICATION OF MYELODYSPLASTIC SYNDROME-SPECIFIC GENES BY DNA MICROARRAY ANALYSIS WITH PURIFIED HEMATOPOIETIC STEM CELL FRACTION" BLOOD, W.B.SAUNDERS COMPAGNY, ORLANDO, FL, US, vol. 98, no. 2, 15 July 2001 (2001-07-15), pages 422-427, XP002952629 ISSN: 0006-4971	
A	MUKAI H Y ET AL: "Elevated serum levels of eosinophil major basic protein in patients with myeloproliferative disorders without eosinophilia." INTERNATIONAL JOURNAL OF HEMATOLOGY. IRELAND AUG 1997, vol. 66, no. 2, August 1997 (1997-08), pages 197-202, XP009021081 ISSN: 0925-5710	
A	WO 97/46885 A (PETERSON CHRISTER ;PHARMACIA & UPJOHN AB (SE); VENGE PER (SE)) 11 December 1997 (1997-12-11)	
P,X	QIAN ZHIJIAN ET AL: "Expression profiling of CD34+ hematopoietic stem/ progenitor cells reveals distinct subtypes of therapy-related acute myeloid leukemia." PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA. UNITED STATES 12 NOV 2002, vol. 99, no. 23, 12 November 2002 (2002-11-12), pages 14925-14930, XP002261373 ISSN: 0027-8424 the whole document	1-3
P,X	NOWICKI MICHAL OSKAR ET AL: "Chronic myelogenous leukemia molecular signature." ONCOGENE. ENGLAND 19 JUN 2003, vol. 22, no. 25, 19 June 2003 (2003-06-19), pages 3952-3963, XP002261374 ISSN: 0950-9232 the whole document	1

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/JP 03/10256

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 13-15  
because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 23-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 21, 27, 28, 32  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1-3, 6-12, 16-26, 28, 30-32 (all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

## Continuation of Box I.1

Although claims 23-29 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

## Continuation of Box I.1

Claims Nos.: 13-15

Rule 39.1(v) PCT - Presentation of information

## Continuation of Box I.2

Claims Nos.: 21,27,28,32

Present claims 21, 27, 28 and 32 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to antisense polynucleotides, small interfering RNA and antibodies.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

Invention 1: claims 1-3, 6-12, 16-26, 28, 30-32 (all partially)

method for diagnosing CML, comprising determining the level of expression of the CML-associated gene CML 1 in a patient, wherein an increase in said level compared to a normal control indicates that said subject suffers from or is at risk of developing CML; method of screening for a compound, which binds, reduces expression or suppresses biological activity of CML 1; methods of treatment and pharmaceutical compositions comprising CML 1 or antisense molecules, siRNAs or antibodies against CML 1

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Inventions 2-190: claims 1-3, 6-12, 16-26, 28, 30-32 (all partially).

method for diagnosing CML, comprising determining the level of expression of the CML-associated gene CML 2-190 in a patient, wherein an increase in said level compared to a normal control indicates that said subject suffers from or is at risk of developing CML; method of screening for a compound, which binds, reduces expression or suppresses biological activity of CML 2-190; methods of treatment and pharmaceutical compositions comprising CML 2-190 or antisense molecules, siRNAs or antibodies against CML 2-190

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Inventions 191-296: claims 1, 4-12, 16-22, 27-29, 32 (all partially)

method for diagnosing CML, comprising determining the level of expression of the CML-associated gene CML 191-296 in a patient, wherein a decrease in said level compared to a normal control indicates that said subject suffers from or is at risk of developing CML; method of screening for a compound, which binds, elevates expression or enhances biological activity of CML 191-296; methods of treatment and pharmaceutical compositions comprising CML 191-296 or a compound that increases expression of CML 191-296

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

PCT/JP 03/10256

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9746885	A	11-12-1997	EP 0927354 A1	07-07-1999
			JP 2000516702 T	12-12-2000
			WO 9746885 A1	11-12-1997
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